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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/623,761	07/21/2003	John H. Laragh	55990/8	4847

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EXAMINER	
SHEN, BIN	
ART UNIT	**PAPER NUMBER**
1657	

NOTIFICATION DATE	DELIVERY MODE
02/25/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/623,761	LARAGH, JOHN H.	
	Examiner	Art Unit	
	BIN SHEN	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 15 Nov 2007 has been entered.

Status of the Claims

Claims 18-21 have been presented for examination.

The previously applied rejection of claims 14-17 under obviousness-type double patenting is withdrawn in view of the terminal disclaimer filed 15 Nov 2007.

Specification

The disclosure is objected to because of the following informalities: The specification at pages 5-6 provides a Brief Description of eight figures, however, no figures were provided according to the transmittal papers. It is believed that these were inadvertently not submitted with this filing as said figures are in the parent application of which this application is a continuation. In providing said drawings, it is noted that Figure 1 appears to disclose prior art, or at least that which was conventionally known in the art about the metabolic pathways involved.

Appropriate correction is required.

Claim Objections

Claims 18-21 are objected to because of the following informalities: the claims recite "PRA" but this term is not clearly defined in the specification as filed. In the parent application, 09860199, PRA was defined as plasma-renin-angiotensin, whereas in the preliminary

amendment to the claims filed 07/21/2003 in the instant application, PRA was defined in claim 15 as plasma- renin activity (consistent with the usage in McMahon below). This discrepancy must be reconciled and a proper definition of this abbreviation provided. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over McMahon (1978). McMahon teaches that some clinics routinely test patients for plasma renin activity, and that these patients fall into three categories: low, medium, and high renin activity hypertensive patients. McMahon teaches that low renin patients can be administered a diuretic alone, i.e., a plasma volume-changing drug. Patients with higher plasma renin activity can be administered renin-blocking or -reducing drugs (see p. 3, for example). McMahon also teaches that it is standard practice, when one drug does not appear to be working, to add a second drug of a different type, i.e. if a diuretic is not working, add a renin-blocking agent, for example (see p. 4, for example). Lastly, McMahon teaches that one should treat the hypertension, not the renin level: because hypertension is a disease of high blood pressure, one must inherently monitor the blood pressure. McMahon also teaches that it is standard practice in treating hypertensive patients to titrate the drug to a proper dosage to eliminate the hypertension; determining proper dosage inherently involves measuring the blood pressure response to a given dosage.

A person of ordinary skill in the art at the time the invention was made would have been motivated to prescribe an anti-renin drug to a patient with medium to high PRA because

McMahon teaches that such patients can be administered such drugs, and alternatively patients with low PRA should be administered diuretic drugs; additionally, McMahon teaches that it is standard practice to titrate dosage to achieve optimal amelioration of hypertensive symptoms, and because that doctors should treat the hypertension, it is inherent that blood pressure should be monitored because hypertension is a disease of high blood pressure.

Hence, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to prescribe a diuretic or renin-blocking drug based on PRA measurement, and to modulate dosages based on blood pressure response to drug administration.

Claims 18-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over McMahon (1978) in view of Laragh (1998).

The teachings of McMahon are discussed above and applied as before.

McMahon does not expressly teach that a threshold level of plasma renin activity is 0.65 ng/ml/h.

Laragh teaches exactly that threshold as a guide for diagnosing primary aldosteronism (see p. 171S, col. 2, for example). Laragh teaches that finding a baseline plasma renin activity for every new patient greatly facilitates drug choice. The goal is to find the primary pressor mechanism: high renin indicates an anti-renin drug, while low renin indicates an antivolume drug. Laragh further teaches that the PRA test guides, simplifies, and hastens the selection of the right single drug for each patient (see p. 171 S, col. 2, for example).

A person of ordinary skill in the art at the time the invention was made would have been motivated to treat a hypertensive with an anti-renin drug if their PRA was greater than 0.65 ng/ml/h because Laragh teaches that below that level the underlying pathology probably involves primary aldosteronism rather than renin-mediated hypertension.

Hence, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to prescribe a renin-blocking drug above 0.65 ng/ml/h PRA.

Applicant's arguments filed 11/15/2007 have been fully considered but they are not persuasive.

Applicants argue that McMahon does not suggest that clinics use renin measurements to direct the specific course of treatment in the pending claims, and McMahon teaches away from the presently claimed invention since McMahon does not recognize that a course of treatment should begin with an initial measurement of a subject's PRA.

At pages 3-4, McMahon states:

A few hypertensive clinics routinely obtain the plasma renin activity (PRA) on all of their patients. Patients must be taken off all antihypertensive drugs for at least two weeks because these drugs greatly effect the PRA levels.

Diuretics and Vasodilators: ↑ PRA

Adrenergic and ß-blockers: ↓ PRA

Then the PRA is determined by radio-immunoassay and correlated with a quantitative 24-hour urinary sodium excretion.[1] In this manner, essential hypertensive patients can be divided into three sub- populations:

1. Low Renin* (About 20-30% of total group);

2. Normal Renin (About 55-65% of total group);

3. High Renin (About 10-15% of total group).

Proponents of the routine use of renin-profiling for all hypertensive patients maintain, that more specific therapy can be selected. At least one group also maintains that the prognosis is more benign in the low-renin hypertensive, although the preponderance of data fails to give any prognostic reassurance to these low-renin individuals.[4 11] Since low renin patients apparently have expanded plasma volume, they respond nicely to diuretics alone. On the opposite end of the spectrum, high renin (hyperreninemic) patients respond well to renin-blocking or -reducing drugs, such as beta-adrenergic blocking agents or adrenergic-blocking agents.

Is it necessary for good therapy to have classified hypertensive patients as to their renin levels? This is still not a resolved issue. If these assays were uniformly accurate, and if 23 million hypertensives could collect a 24-hour urine quantitatively while being offmedication for at least two weeks, and if the several hundred million dollars were available to pay for these tests, one might accurately categorize a given patient as having "low-, normal- or high-renin hypertension", for example, but the Joint National Committee[12] and the vast majority of

physicians usually begin treatment of hypertensive out-patients with a diuretic. Should the patient have high renin essential hypertension, it is more apt to be severe rather than mild and therefore likely to require two or three drugs, one of which would likely be a renin-reducing agent such as a beta-blocking or adrenergic-blocking agent. Should a patient have mild essential high renin hypertension and should he be given diuretics, his poor clinical response would lead to the addition of other agents. For the present, at least, the best advice seems to be -- Treat the hypertension! Don't treat the renin level!

[1]Dustan comments that these patients are frequently tall, obese and drink large quantities of water.

From this discussion in McMahon, it would appear that at the time of writing, PRA levels were not routinely or reliably obtained, and physicians are advised not to administer a diuretic as the first line of treatment because PRA levels are generally not known or not known reliably. Hence the reason McMahon says to treat the hypertension not the renin level is because the PRA levels are not well known generally. It is also clear, that if the PRA level is known reliably, then one can treat high renin patients with renin-blocking agents or adrenergic blocking agents, and low renin patients with diuretics.

It is the examiner's position that McMahon suggests it is possible to categorize a given patient as having "low-, normal- or high-renin hypertension" (page 4, lines 4-5), and McMahon teaches an initial measurement of a subject's PRA two weeks after taken them off from all antihypertensive drugs (page 3, lines 10-12). McMahon also teaches high renin patients respond well to renin-blocking or reducing drugs (page 3, lines 29-31). Therefore it would be obvious to one of ordinary skill in the art at the time the invention was made to measure initial PRA of a patient and treat normal to high PRA patient by administering different dosage of medications because it is common practice to measure blood pressure to monitor the efficacy of the hypertensive treatment (page 4).

Applicants argue that Laragh does not disclose or suggest a course of treatment based on an initial PRA measurement.

It is the examiner's position that McMahon suggests/states that "there is a faction among clinicians that advocates the initial measurement of renin" and "use of renin as a guide to medication", and Laragh teaches that finding a baseline plasma renin activity for every new

patient greatly facilitates drug choice, and that high renin indicates an anti-renin drug, while low renin indicates an antivolume drug, thus the PRA test guides, simplifies, and hastens the selection of the right single drug for each patient (see p. 171 S, col. 2, for example).

Conclusion

No claim is allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1657 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Bin Shen, Ph.D., whose telephone number is (571) 272-9040. The examiner can normally be reached on Monday through Friday, from about 9:00 AM to about 5:30 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to her office).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Jon Weber can be reached at (571) 272-0925.

B Shen

Art Unit 1657

/Jon P Weber/
Supervisory Patent Examiner, Art Unit 1657